

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>4239-55911</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/26689</b>	International filing date (day/month/year) <b>29/09/2000</b>	(Earliest) Priority Date (day/month/year) <b>02/10/1999</b>
Applicant  <b>THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 1-26, 37-41 and 27-32, as far as they refer to an invivo method, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 33-36 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## Continuation of Box I.2

Present claims 1-5, 17, 20-21, 23, 25-26, 33-38 relate to a compound defined by reference to a desirable characteristic or property, namely modulation of FGF-5 expression/activity or modulation of immune response to FGF-5.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunorecative sensitized T cells sensitized with FGF-5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/26689

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K38/18 C07K14/50 A61K39/395 C07K16/22

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 00 24756 A (HUNAN GENOME SCIENCES INC.) 4 May 2000 (2000-05-04) claims 1-23	1-41
X, P	WO 99 55861 A (EISAI CO. LTD.) 4 November 1999 (1999-11-04)  claims 1-19, 23, 24 page 42, line 10 - line 3 page 46, line 20 - page 47, line 26	1-5, 9-14, 23, 24, 27-32, 37-40
X	WO 90 12597 A (THE SALK INSTITUTE FOR BIOLO) 1 November 1990 (1990-11-01) the whole document	1-6, 23, 24, 37-39

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\* & \* document member of the same patent family

Date of the actual completion of the international search

9 July 2001

Date of mailing of the international search report

20/07/2001

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/26689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 05, 30 April 1998 (1998-04-30) & JP 10 017599 A (POLA CHEM IND INC), 20 January 1998 (1998-01-20) abstract	33-36
A	<p style="text-align: center;">---</p> ZHAN X ET AL: "THE HUMAN FGF-5 ONCOGENE ENCODES A NOVEL PROTEIN RELATED TO FIBROBLAST GROWTH FACTORS" MOLECULAR AND CELLULAR BIOLOGY, US, WASHINGTON, DC, vol. 8, no. 8, 1 August 1988 (1988-08-01), pages 3487-3495, XP002034597 ISSN: 0270-7306 abstract	1-41
A	<p style="text-align: center;">---</p> DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; YAMANAKA K. ET AL: "Expression of fibroblast growth factors in human non-papillary renal cell carcinoma: Correlation with tumor progression." retrieved from STN Database accession no. 1999207619 XP002171451 abstract & INTERNATIONAL JOURNAL OF CLINICAL ONCOLOGY, (1999) 4/2 (74-77). ,	1-41
A	<p style="text-align: center;">---</p> DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOSHIMURA, KOJI ET AL: "Messenger ribonucleic acids for fibroblast growth factors and their receptor in bladder and renal cell carcinoma cell lines" retrieved from STN Database accession no. 124:339650 HCA XP002171452 abstract & CANCER LETT. (SHANNON, IREL.) (1996), 103(1), 91-7 ,	1-41
	<p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	





# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/26689

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>           DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            WERNER, SABINE ET AL: "Fibroblast growth            factor 5 proto-oncogene is expressed in            normal human fibroblasts and induced by            serum growth factors"            retrieved from STN            Database accession no. 116:35063 HCA            XP002171453            abstract            &amp; ONCOGENE (1991), 6(11), 2137-44 ,              -----         </p>	1-41



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/26689

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0024756	A	04-05-2000	AU 4688499 A	15-05-2000
WO 9955861	A	04-11-1999	AU 3170499 A	16-11-1999
WO 9012597	A	01-11-1990	US 5191067 A	02-03-1993
			CA 2053275 A,C	28-10-1990
			DE 69010330 D	04-08-1994
			DE 69010330 T	20-10-1994
			EP 0470183 A	12-02-1992
			JP 2891306 B	17-05-1999
			JP 4507093 T	10-12-1992
			US 5576288 A	19-11-1996
			US 5679637 A	21-10-1997
JP 10017599	A	20-01-1998	NONE	



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/13620

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-12, 14-16

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/13620

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-12 and 14-16, drawn to nucleic acid, vector, host cell, polypeptide, methods of making host cell and polypeptide.

Group II, claim 13, drawn to an antibody.

Group III, claim 17, drawn to a method of administering a polypeptide.

Group IV, claim 18, drawn to a method of diagnosis relating to mutations in DNA.

Group V, claim 19, drawn to a method of diagnosis relating to the expression of a polypeptide.

Group VI, claim 20, drawn to a method for identifying binding partners for a polypeptide.

Group VII, claims 21, 22 and 23, drawn to a method for identifying compounds which modulate the cellular response induced by FGFR5.

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: This Authority considers that the main invention in the instant application comprises the first-recited product, polynucleotide encoding FGFR5, and the first-recited method of using that product, namely in the process of producing the encoded polypeptide. Note that there is no method of making the polynucleotide. Also included in this group is the product made, namely the encoded polypeptide, and vector and host cell comprising the polynucleotide. Further, the ISA/US considers that the materially and functionally dissimilar product of group II and the additional methods of groups III-VII do not correspond to the main invention. This Authority therefore considers that the several inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1.

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1	CACCCCAGGTCCCGACACCCCGAGATGACCCCGAGCCCGCTGTGCTGCTCCTGCTGCCG	60
1	M T P S P L L L L L L P	12
61	CCGCTGCTGCTGGGGGCTTCCACCGGCGCCCGCCCGAGGCCCCCAAGATGCCG	120
13	P L L L G A F P P A A A R G P P K M A	32
121	GACAAGGTGCTCCACCGCAGGTGGCCCGGCTGGCCCGCACTGTGCGGCTGGAGTGCCCA	180
33	D K Y V P R Q V A R L G R T V R L Q C P	52
181	GTGGAGGGGAGCCCGCGCCGCTGACCATGTGGACCAAGGATGGCCGACCATCCACAGC	240
53	V E G D P P P L T M W T K D G R T I H S	72
241	GGCTGAGCGGCTTCGGCTGCTGCGCGAGGGCTGAAGGTGAAGCAGGTGAGCGCGAG	300
73	G W S R F R V L P Q G L K V K Q V E R E	92
301	GATGCCCGGCTGTACGTGTGCAAGGCCACCAACGGCTTGGCAGCCTTAGCGTCACTAC	360
93	D A C V Y Y C K A T N G F G S L S V N Y	112
361	ACCCTCGTGCTGCTGGATGACATTAGCCACGGGAAGGAGAGCCTGGGGCCCGACAGCTCC	420
113	T L V V L D D I S P G K E S L G P D S S	132
421	TCTGGGGTCAAGAGACCCCGCCAGCCAGCTGGGCAAGACCGGCTTCACACAGCCC	480
133	S G G Q E D P A S Q Q W A R P R F T Q P	152
481	TCCAAGATGAGGGCGCGGTGATCGCACGGCCCGTGGGTAGCTCCGTGCGGCTCAAGTGC	540
153	S K M R R R V I A R P Y G S S V R L K C	172
541	GTGGCCAGCGGGCACCTCCGCGGACATCAAGTGGATGAAGGACGACCAAGCCTTGAGC	600
173	V A S G H P R P D I T W M K D D Q A L T	192
601	CGCCAGAGGCGGCTGACCCAGGAAGAAGTGGACACTGAGCCTGAAGAAGCTGGGG	660
193	R P E A A E P R K K K W T L S L K N L R	212
661	CCGGAGGACAGCGCAATACACCTGCCGGTGTGCAACCGCGCGGGCCATCAACGCC	720
213	P E D S G K Y T C R V S N R A G A I N A	232
721	ACCTACAAGGTGGATGTGATCCAGCGGACCGTTCCAAGCCCGTGGTCAAGGCACGCAC	780
233	T Y K V D V I Q R T R S K P V L T G T H	252
781	CCCGTGAACACGAGGTGGACTTCGGGGGACCAAGTCCCTCCAGTGAAGGTGGCAGC	840
253	P V N T T V D F G G T T S F Q C K V R S	272
841	CADGTGAAGCGGTGATCCAGTGGCTGAAGCGCGTGGAGTACGGCGCCGAGGGCGCCAC	900
273	D V K P V I Q W L K R V E Y G A E G R H	292
901	AACTCCACCATCGATGTGGGGGGCAGAAGTTTGTGGTGGTGGCCAGGGTGACGTGTGG	960
293	N S T I D V G G Q K F V V L P T G D V W	312

FIG. 1A

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961	TGGCGGCCGACCGCTCCTACCTCAATAAGCTGCTCATCACCGGTGCCCGCCAGGACGAT	1020
313	S R P D G S Y L N K L L I T R A R Q D D	332
1021	GCGGGCATGTACATCTGCCCTTGGCGCCAACACCATGGGCTACAGCTTCGGCAGCGCCTTC	1080
333	A G M Y I C L G A N T M G Y S F R S A F	352
1081	CTCAGCGTCTGCCAGACCCAAAACGGCAAGGGCCACCTGTGGCCTCCTCGTCCTCGGCC	1140
353	L T V L P D P K P Q G P P V A S S S S A	372
1141	ACTAGCGTGGCGTGGCGCGTGGTCACTCGGCATCCCGCGCGCTCTCTTCATCCTGGGC	1200
373	T S L P W P V Y J G J P A G A V F J L G	392
1201	ACCTGCTCCTGTGGCTTGGCAGGCCAGAGAAGCGGTGCACCCCGGGCGCTGCCCT	1260
393	T L L L W L C Q A Q K K P C T P A P A P	412
1261	CGCTGCCCTGGGCACCGCCCGCGGGGACGGCCCTGACCGCAGCGGAGACAAGGACCTT	1320
413	P L P G H R P P G T A L D R S G D K D L	432
1321	CGCTGCTTGGCGCGCTCAGCGCTGGCCCTGGTGTGGCGCTGTGTGAGGAGCATGGCTT	1380
433	P S L A A L S A G P G V G L C E E H G S	452
1381	CGCGCAGCCCGCAGCACTTACTGGGCCCAGGCCAGTTGCTGGCCCTAAGTTGTACCC	1440
453	P A A P Q H L L G P G P V A G P K L Y P	472
1441	AAACTCTACACAGACATCCACACACACACACACACACTCTCACACACACTCACACGTG	1500
473	K L Y T D J H T H T H T H S H T H S H V	492
1501	GAGGCAAGGTCCACACAGCATCCACTATCAGTGCCTAGAGGGCAGGTATCTGCAGTGG	1560
493	E G K V H Q H J H Y Q C *	505
1561	GCACGGGGGGCGCGCCAGACAGGCAGACTGGGAGGATGGAGGACGGAGCTGCAGACGAA	1620
1621	GGCAGGGGACCCATGGGAGGAGGAATGGCCAGCACCCAGGCAGTCTGTGTGTGAGGCA	1680
1681	TAGCCCTTGGACACACACACACAGACACACACTACCTGGATCCATGTATGCACACACA	1740
1741	TGGCGGCACAGTGTCTCCTGAAGGCACAGTADGCACACAGGCACATGCACAGATATGC	1800
1801	CGCTTGGGCACACAGATAAGCTGCCCAAATGCAAGCACAGGCACAGAGACATGCCAGAAC	1860
1861	ATACAAGGACATGCTGCCTGAACATACACAGGCACACCCATGGGCAGATGTGCTGCCTCG	1920

FIG. 1B

SUBSTITUTE SHEET (RULE 25)



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1921 ACACACACACACACAGGATATGCTGTCTGGACGCACACAGTCCAGATATGGTATCCGG 1980  
1981 ACACACACGTGCACAGATATGCTGCCTGGACACACAGATAATGCTGCCTTGACACACACA 2040  
2041 TGCACGGATATTCCTGGACACACACACACACAGGGTGCACAGATATGCTGTCTGGACA 2100  
2101 GGCACACACATGCAGATATGCTGCCTGGACACACACTTCCAGACACAGGTGCACAGCCGC 2160  
2161 AGATATGCTGCCTGGACACACGCAGATATGCTGTCTAGTCACACACACACGCAGACATGC 2220  
2221 TGTCCGGACACACACACAGCATGCACAGATATGCTGTCCGGACACACACAGCAAGCAGAT 2280  
2281 ATGCTGCCTGGACACACACACAGATAATGCTGCCTCAACAGTCACACAGGTGCAGATATT 2340  
2341 GCCTGGACACACACATGTGCACAGATATGCTGTCTGGACATGCACACAGGTGCAGATATG 2400  
2401 CTGTCCGGATACACADGGACACACATGCAGATATCCTGCCTGGGCACACAGTTCGGGA 2460  
2461 CACACATGCACACACAGGTGCAGATATCCTGCCTGGACACAGGCAGACTGAGGTGCTTTT 2520  
2521 GGGAGGGTGTGCGGTGAAGCCTGCAGTACGTGTGCGGTGAGGCTCATAGTTGATGACGGA 2580  
2581 CTTTCCCTGCTCCACCGTCACTCCCCAACTCTGCCCCGCTCTGTCCCCGCTCAGTCCC 2640  
2641 CCGCTCCATCCCCGCTCTGTCCCCTGGCCTTGGGGGCTATTTTGGCCACCTGCCTTGG 2700  
2701 TGGCCAGGAGTCCCTACTGCTGTGGGTGCGGTGGGGGACAGCAGCCCCCAAGCCTGA 2760  
2761 GAGGCTGGAGGCCATGGCTAGTGGCTCATCCCCACTGCATTCTCCCCCTGACACAGAGAA 2820  
2821 GGGGCGCTTGGTATTTATATTTAAGAAATGAAGATAATATTAATAATGATCGAAGGAAGAC 2880  
2881 TGGGTTCACGGAGTGTGGTCTCTCCTGGGGCCCGGACCCGCTGGTCTTTGAGCCATG 2940  
2941 CTGATGACACACAGCCGTCACAGCCAGACACCAACCCCAACCCCACTGTCTGTGGTGGCC 3000  
3001 CAGATCTCTGTAATTTTATGTAGAGTTTGAGCTGAAGCCCGGTATATTAAATTTATTTT 3060  
3061 TTAAACATGAAAGTGCATCCTTCCCTCCAAAAAAAAAAAAAAAAAAAAAA 3112

FIG. 1C

1	10	20	30	40	50	60	FGFR5.prot
I	11	21	31	41	51	61	FGFR4prot
51	70	80	90	100	110	120	FGFR5.prot
57	71	81	91	101	111	121	FGFR4prot
111	130	140	150	160	170	180	FGFR5.prot
112	131	141	151	161	171	181	FGFR4prot
170	190	200	210	220	230	240	FGFR5.prot
170	191	201	211	221	231	241	FGFR4prot
227	250	260	270	280	290	300	FGFR5.prot
230	251	261	271	281	291	301	FGFR4prot
287	310	320	330	340	350	360	FGFR5.prot
288	311	321	331	341	351	361	FGFR4prot
346	370	380	390	400	410	420	FGFR5.prot
341	371	381	391	401	411	421	FGFR4prot
360	430	440	450	460	470	480	FGFR5.prot
401	431	441	451	461	471	481	FGFR4prot

FIG. 2A

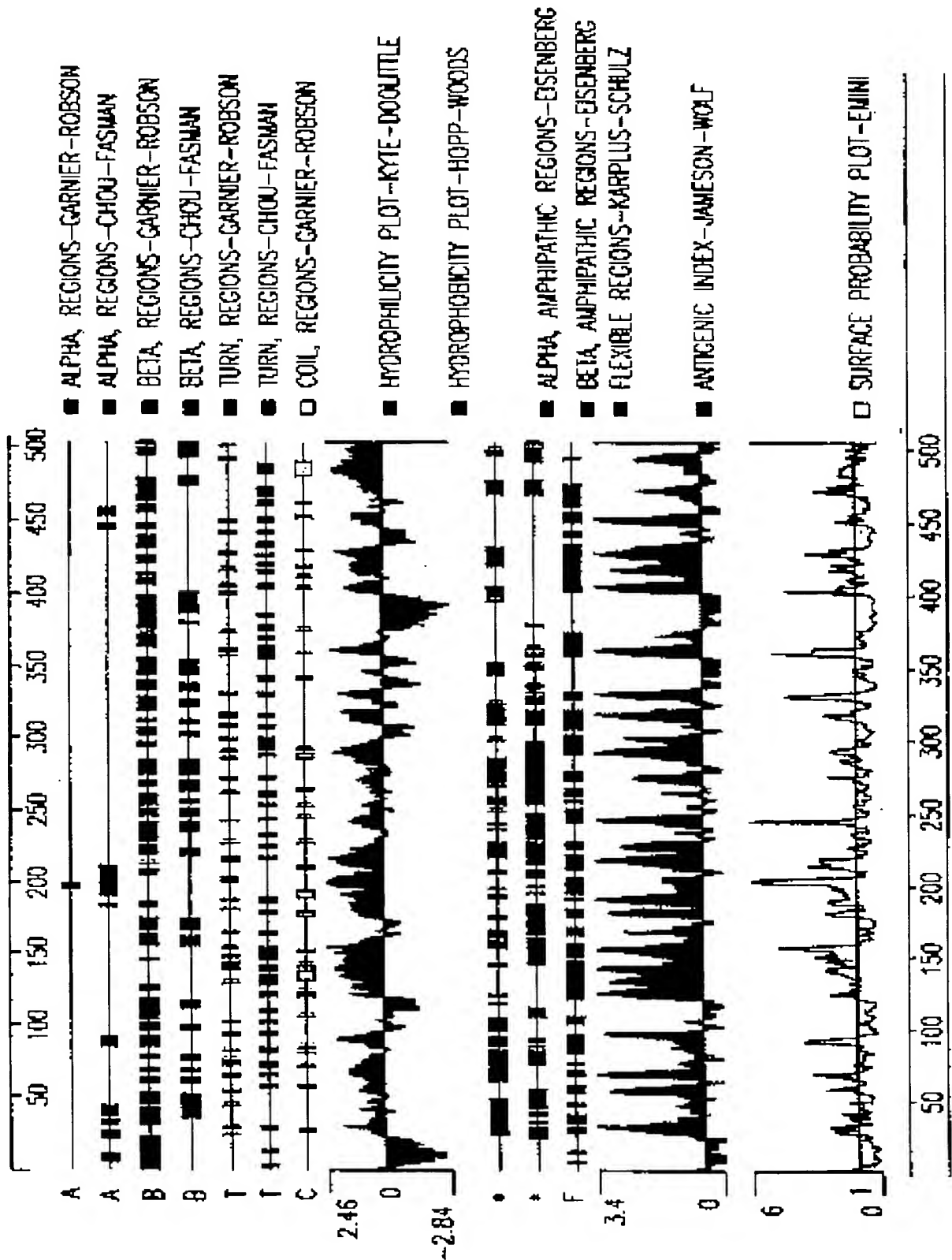
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396	490	500	510	520	530	540	FGFR5_prot
459	LCQKDK--KCTAPPPLP	STYAVXMLKDNASDKDLADV					FGFR4_prot
	DEFP8DRLVLGKPLGEGCFGQVVR	EAFGNDPAREDDQ					
	550	560	570	580	590	600	FGFR5_prot
416					GHPPPTA	DRSE	FGFR4_prot
519	SENEVMXLI6RHKNIINLLGVCTQEGPLYVIVECAK6MLREFLRAR	SPD					
	610	620	630	640	650	660	FGFR5_prot
429			B--DK	PSLAA	SAGPGG	GLCEEH	FGFR4_prot
579	SSEGPLSFPVLVSCAYQVARGMQYLESRKCIHR	AARNV	VTEDM	MKIADF	LARGVH		
	670	680	690	700	710	720	FGFR5_prot
458					DPGFA		FGFR4_prot
639	IDYYKXTSWGRLPVKNNAPCALFORVYTHQSDVWSFGILLWEIFT	EGSPYP	QIPVEEL				
	730	740	750	760	770	780	FGFR5_prot
468		PKL				PKLT	FGFR4_prot
699	FSLLREGHRMDRPPHCP	EL	GLMRECHHAAPSQRPTFKQLVEALDKVLLAVSEEL	LLDLR			
	790	800	810	820			FGFR5_prot
480		THTHSHSHSHVVEGKHQ				IHYQC	FGFR4_prot
759	LTGPPYSPSGGDAASSTGSSDS	FS	DPPLPLGSSSFPEGS5V9T				

FIG. 2B

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FIG. 3



SUBSTITUTE SHEET (RULE 26)

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Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi_	James_ Antig_	Emini Surfa_
Met	1	.	.	B	.	.	.	.	0.31	.	.	.	0.05	1.11
Thr	2	.	.	B	.	.	T	.	-0.11	.	.	.	0.25	1.34
Pro	3	.	.	B	.	.	T	.	-0.53	.	.	.	-0.20	0.87
Ser	4	.	.	B	.	.	T	.	-0.96	.	.	.	-0.20	0.72
Pro	5	.	.	B	.	.	T	.	-1.38	.	.	F	-0.05	0.41
Leu	6	.	A	B	.	.	.	.	-1.53	.	.	F	-0.45	0.22
Leu	7	.	A	B	.	.	.	.	-2.09	.	.	.	-0.60	0.14
Leu	8	.	A	B	.	.	.	.	-2.09	.	.	.	-0.60	0.07
Leu	9	.	A	B	.	.	.	.	-2.00	.	.	.	-0.60	0.14
Leu	10	.	A	B	.	.	.	.	-2.60	.	.	.	-0.60	0.25
Leu	11	.	A	B	.	.	.	.	-2.60	.	.	.	-0.60	0.25
Pro	12	.	A	B	.	.	T	.	-2.60	.	.	F	-0.05	0.25
Pro	13	.	.	B	.	.	T	.	-2.13	.	.	F	-0.05	0.25
Leu	14	.	.	B	.	.	T	.	-1.91	.	.	.	-0.20	0.30
Leu	15	.	.	B	.	.	T	.	-1.80	.	.	.	-0.20	0.20
Leu	16	.	.	B	.	.	.	.	-1.20	.	.	.	-0.40	0.11
Gly	17	.	.	B	.	.	.	.	-1.20	.	.	.	-0.40	0.21
Ala	18	.	.	B	.	.	.	.	-1.58	.	.	.	-0.40	0.39
Phe	19	.	.	B	.	.	.	.	-1.36	.	.	.	-0.40	0.48
Pro	20	.	A	B	.	.	.	.	-1.13	.	.	.	-0.40	0.49
Pro	21	.	A	B	.	.	.	.	-0.91	.	.	.	-0.60	0.49
Ala	22	.	A	B	.	.	.	.	-0.46	.	.	.	-0.60	0.57
Ala	23	.	A	B	.	.	.	.	-0.21	.	*	.	0.30	0.72
Ala	24	.	A	B	.	.	.	.	0.28	.	*	.	0.30	0.46
Ala	25	.	A	.	.	T	.	.	0.28	*	*	.	0.70	0.71

FIG. 4A

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Res	Pos	Garni_ Alpha	Chou- Alpha	Garni_ Beta	Chou- Beta	Garni_ Turn	Chou- Turn	Garni_ Coil	Kyle- Hydro	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi	Jones_ Antig	Emini_ Surfa
Arg	26	.	A	.	.	.	.	C	0.53	*	*	F	1.14	1.08
Gly	27	.	A	.	.	.	.	C	0.52	*	*	F	1.78	2.15
Pro	28	.	.	.	.	.	I	C	0.52	*	*	F	2.52	2.10
Pro	29	.	.	.	.	.	I	C	1.11	*	*	F	2.86	1.08
Lys	30	.	.	.	.	.	T	.	1.74	*	*	F	3.40	1.83
Met	31	.	.	B	.	.	T	.	0.78	*	*	.	2.51	2.37
Ala	32	.	A	B	.	.	.	.	0.27	*	.	F	1.77	1.14
Asp	33	.	A	B	.	.	.	.	0.27	*	*	F	1.43	0.42
Lys	34	.	A	B	.	.	.	.	0.59	*	*	F	0.79	0.66
Val	35	.	A	B	.	.	.	.	0.54	*	.	F	0.90	1.28
Val	36	.	.	B	B	.	.	.	0.29	*	.	F	0.90	1.32
Pro	37	.	.	B	B	.	.	.	0.29	*	*	F	0.45	0.49
Arg	38	.	A	B	B	.	.	.	0.40	*	*	F	-0.15	0.67
Gln	39	.	A	B	B	.	.	.	-0.46	*	*	.	0.45	1.77
Val	40	.	A	B	B	.	.	.	0.06	*	.	.	0.30	0.94
Ala	41	.	A	B	B	.	.	.	1.02	*	.	.	0.30	0.48
Arg	42	.	A	B	B	.	.	.	0.92	*	.	.	0.30	0.54
Leu	43	.	A	B	B	.	.	.	-0.04	*	*	.	0.45	1.05
Gly	44	.	A	B	B	T	.	.	0.07	*	*	F	0.85	0.77
Arg	45	.	.	B	B	.	.	.	0.11	*	*	F	0.75	0.77
Thr	46	.	.	B	B	.	.	.	0.70	*	*	F	0.45	0.77
Val	47	.	.	B	B	.	.	.	-0.08	*	*	.	0.45	1.35
Arg	48	.	.	B	B	.	.	.	0.52	*	*	.	0.30	0.37
Leu	49	.	.	B	B	.	.	.	0.01	*	*	.	-0.30	0.39
Gln	50	.	.	B	B	.	.	.	-0.10	*	*	.	0.00	0.39

FIG. 4B

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Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi	James_ Antig	Emmi_ Surfa
Cys	51			B	B				-0.13		*		0.90	0.35
Pro	52			B	B				0.72		*		0.60	0.42
Val	53					T			0.40		*		2.40	0.40
Glu	54					T			1.00		*	F	3.00	1.16
Gly	55					T			0.79		*	F	2.70	1.16
Asp	56						T	C	0.64			F	2.40	2.43
Pro	57						T	C	0.54			F	2.10	1.16
Pro	58						T	C	0.80			F	1.50	1.68
Pro	59						T	C	0.51			F	0.45	1.00
Leu	60			B	B				0.54				-0.60	0.68
Thr	61			B	B				0.59				-0.26	0.63
Met	62			B	B				0.80	*			0.08	0.82
Trp	63			B	B				0.67	*			0.87	1.66
Thr	64			B	B		T		0.99	*		F	2.36	1.14
Lys	65					T	T		1.49	*		F	3.40	2.25
Asp	66					T	T		0.91	*		F	3.06	3.09
Gly	67					T	T		1.48	*		F	2.72	1.50
Arg	68			B	B				1.47	*		F	1.58	1.02
Thr	69			B	B				1.43	*		F	1.09	0.82
Ile	70			B	B				1.10	*			0.30	0.82
His	71						T	C	0.80	*			0.30	0.44
Ser	72						T	C	1.26	*			0.00	0.41
Gly	73					T	T		0.44	*	*	F	0.80	1.14
Trp	74					T	T		0.87	*	*	F	0.65	0.73
Ser	75				B			C	0.90	*	*		0.65	1.06

FIG. 4C

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Res	Pos	Garni_ Alpha	Chou- Alpha	Garni_ Beta	Chou- Beta	Garni_ Turn	Chou- Turn	Garni_ Coil	Kyte- Hydro	Eisen_ Alpha	Eisen_ Beta	Karpt_ Flexi	James_ Anti	Emini_ Surfa
Arg	76				B	T			0.12	*	*		0.10	0.80
Phe	77			B	B				0.21	*	*		-0.60	0.62
Arg	78			B	B				0.56	*	*		0.30	0.72
Val	79			B	B				0.50	*	*		0.30	0.64
Leu	80			B	B				-0.01	*	*		-0.30	0.73
Pro	81						T	C	-0.06	*	*	F	0.45	0.31
Gln	82					T			-0.23	*	*	F	0.65	0.83
Gly	83					T		C	-0.30	*	*	F	0.45	0.74
Leu	84					T		C	0.56			F	1.05	0.96
Lys	85		A	B					0.51			F	0.45	0.96
Val	86		A	B					0.72	*	*	F	0.45	0.72
Lys	87		A	B					0.83	*	*	F	0.90	1.51
Gln	88		A	B					1.18	*	*	F	0.90	1.48
Val	89		A	B					1.99	*	*	F	0.90	3.46
Glu	90		A	B					1.36	*	*	F	1.21	2.89
Arg	91		A	B					1.87	*	*	F	1.52	1.69
Glu	92		A	B					0.97	*	*	F	1.83	2.25
Asp	93					T			0.72			F	2.79	0.96
Ala	94					T			0.72			F	3.10	0.77
Gly	95					T			0.06				2.34	0.33
Val	96			B			T		-0.01	*	*		0.73	0.11
Tyr	97			B	B				-0.60	*	*		0.02	0.21
Val	98			B	B				-0.91	*	*		-0.29	0.21
Cys	99			B	B				-0.32				-0.60	0.42
Lys	100			B	B				-0.32	*	*		-0.30	0.43

FIG. 4D



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Res	Pos	Garni_ Alpha	Chou- Alpha	Garni_ Beta	Chou- Beta	Garni_ Turn	Chou- Turn	Garni_ Coil	Kyle- Hydro	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi	James_ Antig	Emini_ Surfa
Ala	101			B			T		-0.17	*		F	0.25	0.57
Thr	102			B			T		-0.27	*		F	0.25	0.92
Asn	103					T	T		0.29	*		F	0.65	0.46
Gly	104					T	T		0.14	*		F	0.35	0.60
Phe	105			B				C	-0.20	*		F	-0.25	0.35
Gly	106								-0.47		*		-0.05	0.29
Ser	107			B					-0.16		*		-0.40	0.22
Leu	108			B					-0.40		*		-0.40	0.40
Ser	109			B			T		-0.37		*		-0.20	0.63
Val	110			B			T		-0.48		*		-0.20	0.58
Asn	111			B			T		-0.99		*		-0.20	0.68
Tyr	112			B			T		-1.54		*		-0.20	0.38
Thr	113			B	B				-1.54		*		-0.60	0.38
Leu	114			B	B				-1.24				-0.60	0.19
Val	115			B	B				-0.39	*			-0.60	0.21
Val	116			B	B				-1.28	*			-0.30	0.24
Leu	117			B	B				-1.33				-0.30	0.20
Asp	118			B	B				-1.23			F	-0.15	0.37
Asp	119			B	B				-0.77			F	0.99	0.77
Ile	120			B					0.13	*		F	1.33	0.92
Ser	121						T	C	0.99	*		F	2.52	1.10
Pro	122						T	C	1.50	*		F	2.86	1.14
Gly	123					T	T		0.69	*		F	3.40	2.18
Lys	124						T	C	0.34			F	2.86	1.34
Glu	125			B					1.02			F	1.97	0.86

FIG. 4E

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Res	Pos	Gorni_ Alpha	Chou_ Alpha	Gorni_ Beta	Chou_ Beta	Gorni_ Turn	Chou_ Turn	Gorni_ Coil	Kyle_ Hydro	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi	James_ Antig	Emini Surfa
Ser	126	.	.	B	.	.	.	.	1.32	.	.	F	1.78	1.34
Leu	127	.	.	B	.	.	.	.	1.23	.	.	F	1.74	1.12
Gly	128	.	.	B	.	.	T	.	1.28	.	.	F	1.75	0.87
Pro	129	.	.	.	.	.	T	C	0.93	.	.	F	1.95	0.87
Asp	130	.	.	.	.	T	T	C	0.59	.	.	F	2.60	1.41
Ser	131	.	.	.	.	.	T	C	0.54	.	.	F	3.00	1.41
Ser	132	.	.	.	.	.	T	C	1.36	.	.	F	2.55	0.90
Ser	133	.	.	.	.	.	T	C	1.70	.	.	F	2.25	0.94
Gly	134	.	.	.	.	.	T	C	1.91	.	.	F	2.10	1.21
Gly	135	.	.	.	.	.	T	C	1.70	.	.	F	1.80	1.51
Gln	136	.	.	.	.	.	.	C	1.41	.	.	F	1.64	1.74
Glu	137	.	.	.	.	.	.	C	1.41	.	.	F	1.98	1.77
Asp	138	.	.	.	.	.	T	C	1.71	.	.	F	2.52	2.40
Pro	139	.	.	.	.	.	T	C	2.06	.	.	F	2.86	2.40
Ala	140	.	.	.	.	.	T	C	2.11	.	.	F	3.40	2.40
Ser	141	.	.	.	.	T	T	C	1.52	.	.	F	1.96	1.51
Gln	142	.	.	B	.	.	.	.	1.63	*	.	F	0.77	0.99
Gln	143	.	.	.	.	T	.	.	1.42	*	.	F	1.28	1.92
Irp	144	.	.	.	.	T	.	.	1.74	.	*	F	0.94	2.21
Ala	145	.	.	B	.	.	.	.	1.63	.	*	.	0.65	2.50
Arg	146	.	.	B	.	.	T	.	1.62	.	*	.	0.25	1.25
Pro	147	.	.	B	.	T	T	.	1.62	.	*	F	0.40	1.72
Arg	148	.	.	.	.	T	T	.	1.41	.	*	F	1.40	2.94
Phe	149	.	.	.	.	T	T	.	1.40	.	*	F	1.74	2.32
Thr	150	.	.	.	.	.	.	C	2.03	.	*	F	1.68	2.01

FIG. 4F

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Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi_	James_ Antig_	Emni Surfa_
Gln	151	.	.	.	.	.	T	C	1.32	.	*	F	2.52	2.06
Pro	152	.	.	.	.	.	T	C	1.64	.	*	F	1.96	2.35
Ser	153	.	.	.	.	T	T	.	1.64	*	*	F	3.40	3.19
Lys	154	.	.	.	.	T	T	.	2.46	*	*	F	3.06	3.61
Met	155	.	.	B	.	.	.	.	1.91	*	*	F	2.12	4.57
Arg	156	.	.	B	B	.	.	.	1.02	*	*	F	1.58	2.53
Arg	157	.	.	B	B	.	.	.	0.64	*	*	F	1.09	0.89
Arg	158	.	.	B	B	.	.	.	1.06	*	*	.	0.60	0.91
Val	159	.	.	B	B	.	.	.	0.80	*	*	.	0.60	0.91
Ile	160	.	.	B	B	.	.	.	0.54	.	*	.	0.60	0.71
Ala	161	.	.	B	B	.	.	.	0.09	*	*	.	0.55	0.27
Arg	162	.	.	B	B	.	.	.	-0.32	*	.	.	0.20	0.36
Pro	163	.	.	B	B	.	T	.	-0.73	*	*	F	1.00	0.69
Val	164	.	.	.	.	T	T	.	-0.73	*	*	F	2.25	0.92
Gly	165	.	.	.	.	T	T	.	0.27	*	*	F	2.50	0.35
Ser	166	.	.	B	.	.	T	.	0.04	*	*	F	1.85	0.44
Ser	167	.	.	B	B	.	.	.	-0.02	.	*	F	0.60	0.49
Val	168	.	.	B	B	.	.	.	-0.48	.	*	F	0.95	0.99
Arg	169	.	.	B	B	.	.	.	-0.48	.	*	.	0.55	0.39
Leu	170	.	.	B	B	.	.	.	-0.72	.	*	.	0.30	0.22
Lys	171	.	.	B	B	.	.	.	-0.72	.	*	.	-0.30	0.30
Cys	172	.	.	B	B	.	.	.	-0.77	.	*	.	0.30	0.20
Val	173	.	.	B	B	.	.	.	0.06	.	*	.	-0.30	0.24
Ala	174	.	.	B	B	.	.	.	-0.27	*	*	.	0.00	0.17
Ser	175	.	.	B	B	.	.	.	0.66	*	*	.	0.00	0.48

FIG. 4G

14/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyle_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jones_ Antig_	Emini Surfo_
Gly	176	.	.	.	.	.	.	C	0.40	*	*	F	1.90	1.27
His	177	.	.	.	.	.	T	C	1.07	.	*	F	2.40	1.94
Pro	178	.	.	.	.	.	T	C	1.03	.	*	F	3.00	2.41
Arg	179	.	.	.	.	.	T	C	1.31	.	*	F	2.70	1.71
Pro	180	.	.	.	.	T	T	.	1.32	.	*	F	2.30	1.81
Asp	181	.	.	.	.	T	.	.	1.07	.	*	F	1.80	1.23
Ile	182	.	A	B	.	.	.	.	1.14	*	*	.	0.00	0.62
Thr	183	.	A	B	.	.	.	.	1.36	*	*	.	0.04	0.81
Trp	184	.	A	B	.	.	.	.	1.24	.	*	.	0.98	0.81
Met	185	.	A	B	.	.	.	.	1.46	.	.	.	1.47	1.92
Lys	186	.	.	B	.	.	T	.	0.87	.	.	.	2.51	2.30
Asp	187	.	.	.	.	T	T	.	0.94	.	.	F	3.40	2.21
Asp	188	.	.	.	.	T	T	.	0.94	*	.	F	3.06	1.84
Gln	189	.	.	.	.	.	T	C	1.34	*	.	F	2.52	1.33
Ala	190	.	A	.	.	.	.	C	1.73	*	.	.	1.63	1.56
Leu	191	.	A	.	.	.	.	C	1.69	*	*	F	1.14	1.45
Thr	192	.	A	.	.	.	.	C	1.10	.	*	F	0.80	1.45
Arg	193	.	A	.	.	.	.	C	0.51	.	.	F	0.80	1.45
Pro	194	.	A	.	.	.	.	C	0.51	.	.	F	0.80	1.77
Glu	195	A	A	.	.	.	.	C	0.89	*	.	F	0.90	2.13
Ala	196	A	A	.	.	.	.	.	1.81	*	.	F	0.90	1.68
Ala	197	A	A	.	.	.	.	.	2.17	.	*	F	0.90	2.13
Glu	198	A	A	.	.	.	.	.	2.10	.	.	F	0.90	2.45
Pro	199	A	A	.	.	.	.	.	2.36	.	.	F	0.90	4.86
Arg	200	.	A	.	.	T	.	.	2.07	.	.	F	1.30	9.62

FIG. 4H

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Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi_	James_ Antig_	Emini Surfa_
Lys	201	A	A	.	.	.	.	.	2.34	.	.	F	0.90	5.84
Lys	202	.	A	.	.	I	.	.	2.12	.	.	F	1.30	5.45
Lys	203	.	A	.	.	I	.	.	1.82	.	*	F	1.30	2.29
Trp	204	.	A	B	.	.	.	.	1.22	.	*	.	0.75	1.54
Thr	205	.	A	B	.	.	.	.	1.16	.	*	.	-0.30	0.63
Leu	206	.	A	B	.	.	.	.	1.11	*	*	.	-0.30	0.63
Ser	207	.	A	B	.	.	.	.	0.26	*	.	.	-0.60	0.97
Leu	208	.	A	B	.	.	.	.	0.32	*	*	.	-0.30	0.55
Lys	209	.	A	B	.	.	.	.	0.40	*	*	F	1.00	1.32
Asn	210	.	A	.	.	.	.	C	0.71	.	.	F	0.80	1.52
Leu	211	.	A	.	.	.	.	C	1.52	.	.	F	1.44	3.19
Arg	212	.	A	B	.	.	.	.	1.52	.	.	F	1.58	2.66
Pro	213	.	.	B	.	.	.	.	1.99	.	*	F	2.12	2.22
Glu	214	.	.	B	.	.	.	.	1.99	.	*	F	2.86	2.66
Asp	215	.	.	.	.	.	T	.	1.74	.	*	F	3.40	2.72
Ser	216	.	.	.	.	.	T	.	2.24	.	*	F	3.06	2.76
Gly	217	.	.	.	.	.	T	.	1.47	*	*	F	2.72	2.30
Lys	218	.	.	.	.	.	T	.	1.79	*	*	F	1.93	0.74
Tyr	219	.	.	B	B	.	.	.	0.93	*	*	F	0.94	1.08
Thr	220	.	.	B	B	.	.	.	0.63	*	*	.	0.56	0.81
Cys	221	.	.	B	B	.	.	.	0.93	*	*	.	0.82	0.54
Arg	222	.	.	B	B	.	.	.	1.39	*	*	.	0.48	0.56
Val	223	.	.	B	B	.	T	.	0.76	*	*	.	2.04	0.75
Ser	224	.	.	B	B	.	T	.	0.66	*	*	F	2.60	1.42
Asn	225	.	.	B	B	.	T	.	0.38	*	*	F	2.19	0.72
Arg	226	.	.	.	.	.	T	.	0.16	*	*	F	2.03	0.98

FIG. 4I

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Res	Pos	Gorni_ Alpha	Chou_ Alpha	Gorni_ Beta	Chou_ Beta	Gorni_ Turn	Chou_ Turn	Gorni_ Coil	Kyle_ Hydro	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi	James_ Antig	Emini_ Surfa
Ala	227	.	.	.	.	T	.	C	0.04	*	*	F	1.57	0.51
Gly	228	.	.	.	.	.	.	C	0.31	.	.	.	0.96	0.51
Ala	229	.	.	B	.	.	.	.	0.30	.	.	.	-0.10	0.26
Ile	230	.	.	B	.	.	.	.	0.06	.	*	.	-0.40	0.38
Asn	231	.	.	B	.	.	I	.	-0.01	.	*	.	-0.20	0.60
Ala	232	.	.	B	.	.	I	.	-0.28	.	*	.	0.25	1.18
Thr	233	.	.	B	.	.	I	.	0.07	.	*	.	-0.05	1.25
Tyr	234	.	.	B	.	.	I	.	-0.20	.	*	.	0.85	1.30
Lys	235	.	.	B	B	.	.	.	-0.20	.	*	.	-0.30	0.95
Val	236	.	.	B	B	.	.	.	-0.20	*	*	.	-0.30	0.46
Asp	237	.	.	B	B	.	.	.	0.50	*	*	.	-0.30	0.51
Val	238	.	.	B	B	.	.	.	0.50	.	*	.	0.60	0.50
Ile	239	.	.	B	B	.	.	.	0.86	.	*	.	0.64	0.98
Gln	240	.	.	B	B	.	.	.	0.51	*	*	.	1.43	1.14
Arg	241	.	.	B	B	.	.	.	1.41	*	*	F	1.62	2.06
Thr	242	.	.	.	.	I	I	.	1.20	*	*	F	3.06	5.89
Arg	243	.	.	.	.	T	T	C	1.20	.	*	F	3.40	5.26
Ser	244	.	.	.	.	.	I	.	1.28	.	*	F	2.86	1.99
Lys	245	.	.	.	.	.	T	C	0.97	.	*	F	2.22	1.14
Pro	246	.	.	B	B	.	.	.	0.51	.	*	F	1.13	0.84
Val	247	.	.	B	B	.	.	.	0.51	.	*	F	0.19	0.62
Leu	248	.	.	B	B	.	.	.	0.37	.	*	F	-0.15	0.45
Thr	249	.	.	B	B	.	.	.	0.46	*	.	F	-0.45	0.39
Gly	250	.	.	B	B	.	.	.	-0.44	*	.	F	-0.45	0.82
Thr	251	.	.	B	B	.	.	.	-0.23	.	.	F	-0.45	0.74

FIG. 4J

17/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi_	James_ Antig_	Emini_ Surfo_
His	252	.	.	.	.	.	T	C	0.31	.	.	F	0.45	0.82
Pro	253	.	.	.	.	.	T	C	0.81	.	.	.	0.45	1.20
Val	254	.	.	B	.	.	T	.	0.27	*	*	.	-0.05	1.20
Asn	255	.	.	B	.	.	T	.	0.61	*	*	F	-0.05	0.65
Thr	256	.	.	B	B	.	.	.	0.22	*	*	F	-0.15	0.71
Thr	257	.	.	B	B	.	.	.	-0.09	*	*	F	-0.45	0.82
Val	258	.	.	B	B	.	.	.	-0.22	*	*	.	-0.30	0.51
Asp	259	.	.	B	.	.	T	.	0.32	*	*	.	0.10	0.35
Phe	260	.	.	B	.	T	T	.	0.01	.	.	F	0.25	0.35
Gly	261	.	.	.	.	T	T	.	0.02	.	.	F	0.65	0.68
Gly	262	.	.	.	.	T	T	.	-0.37	.	*	F	1.25	0.54
Thr	263	.	.	.	B	.	.	C	0.49	.	*	F	-0.25	0.54
Thr	264	.	.	.	B	.	.	C	-0.18	.	*	F	0.05	0.95
Ser	265	.	.	.	B	.	.	C	0.57	.	*	F	-0.25	0.51
Phe	266	.	.	B	B	.	.	.	0.06	*	*	.	-0.15	0.71
Gln	267	.	.	B	B	.	.	.	0.51	*	*	.	0.00	0.37
Cys	268	.	.	B	B	.	.	.	0.52	.	*	.	0.75	0.54
Lys	269	.	.	B	B	.	.	.	0.83	*	*	.	0.90	0.83
Val	270	.	.	B	B	.	T	.	0.28	*	*	F	1.50	0.80
Arg	271	.	.	B	.	T	T	.	1.02	*	*	F	1.90	1.11
Ser	272	.	.	.	.	T	T	.	0.81	*	*	F	2.15	1.11
Asp	273	.	.	.	.	T	T	.	0.62	*	*	F	2.00	2.31
Val	274	.	.	B	.	.	T	.	-0.31	*	*	F	1.30	0.87
Lys	275	.	.	B	B	.	.	.	0.54	*	*	F	0.45	0.46
Pro	276	.	.	B	B	.	.	.	0.14	*	*	F	0.45	0.47

FIG. 4K

18/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi	Jones_ Antig	Emmi_ Surfa
Val	277	.	.	B	B	.	.	.	-0.37	*	*	.	-0.60	0.67
Ile	278	.	.	B	B	.	.	.	-0.32	*	*	.	-0.60	0.28
Gln	279	.	.	B	B	.	.	.	0.64	*	*	.	-0.60	0.36
Trp	280	.	.	B	B	.	.	.	-0.26	*	*	.	-0.30	0.95
Leu	281	.	.	B	B	.	.	.	-0.04	*	*	.	-0.15	1.00
Lys	282	.	.	B	B	.	.	.	0.57	*	*	.	0.45	1.00
Arg	283	.	.	B	B	.	.	.	1.11	*	*	.	0.45	1.49
Val	284	.	.	B	B	.	.	.	0.52	*	*	.	0.45	1.79
Glu	285	.	.	B	B	.	.	.	0.81	*	*	.	0.60	0.90
Tyr	286	.	.	.	.	T	.	C	1.28	*	*	.	1.54	0.80
Gly	287	.	.	.	.	.	T	C	1.34	.	*	.	1.73	1.07
Ala	288	.	.	.	.	.	T	C	1.20	.	*	F	2.52	1.21
Glu	289	.	.	.	.	.	T	C	2.06	.	*	F	2.56	1.05
Gly	290	.	.	.	.	T	T	.	1.76	.	*	F	3.40	1.70
Arg	291	.	.	.	.	T	.	.	1.69	.	*	F	2.86	2.26
His	292	.	.	.	.	.	T	C	1.14	.	*	F	2.52	1.88
Asn	293	.	.	.	.	.	T	C	1.73	.	*	F	1.88	1.33
Ser	294	.	.	B	.	.	T	.	0.88	.	*	F	1.64	1.14
Thr	295	.	.	B	.	.	T	.	0.88	.	*	F	0.25	0.62
Ile	296	.	.	B	.	.	.	.	0.42	*	*	F	0.30	0.38
Asp	297	.	.	B	.	.	T	.	0.46	.	*	F	0.75	0.28
Val	298	.	.	B	.	.	T	.	0.50	*	*	F	1.00	0.34
Gly	299	.	.	.	.	T	T	.	0.10	*	.	F	2.25	0.96
Gly	300	.	.	.	.	T	T	.	-0.44	.	.	F	2.50	0.50
Gln	301	.	.	B	B	.	.	.	-0.41	*	.	F	0.85	0.50

FIG. 4L



19/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi	James_ Antig	Emini_ Surfo
Lys	302			B	B				-1.22			F	0.60	0.37
Phe	303			B	B				-0.58				-0.10	0.31
Val	304			B	B				-0.54				-0.35	0.28
Val	305			B	B				-0.54				-0.60	0.20
Leu	306			B	B		T		-0.54				-0.20	0.23
Pro	307			B	B		T		-1.44			F	0.25	0.52
Thr	308					T	T		-1.03			F	0.65	0.52
Gly	309					T	T		-0.48	*	*	F	0.35	0.66
Asp	310				B	T			0.49	*	*	F	0.25	0.57
Val	311			B	B				1.09		*	F	0.45	0.78
Trp	312			B	B				1.30	*	*	F	0.94	1.21
Ser	313			B	B				1.27	*	*	F	1.58	1.21
Arg	314			B	B		T		1.31	*	*	F	2.02	1.62
Pro	315					T	T		1.07	*	*	F	2.76	2.06
Asp	316					T	T		1.11	*	*	F	3.40	2.41
Gly	317					T	T		1.40	*	*	F	2.76	1.01
Ser	318					T			1.74	*	*	F	1.62	1.06
Tyr	319			B					0.82	*	*	F	1.48	1.26
Leu	320			B					0.22			F	0.54	1.05
Asn	321			B					-0.67	*	*		-0.40	0.65
Lys	322			B	B				-0.63				-0.60	0.29
Leu	323			B	B				-0.22				-0.60	0.51
Leu	324			B	B				-0.57	*	*		0.30	0.52
Ile	325			B	B				0.36	*	*		-0.30	0.31
Thr	326			B	B				0.36		*		0.04	0.74

FIG. 4M

20/26

Res	Pos	Gorni_ Alpha	Chou- Alpha	Gorni_ Beta	Chou- Beta	Gorni_ Turn	Chou- Turn	Gorni_ Coil	Kyle- Hydro-	Eisen_ Alpha	Eisen_ Beta	Korpi_ Flexi-	James_ Antig-	Emmi_ Surfa-
Arg	327	.	.	B	B	.	.	.	0.31	.	*	F	1.28	1.56
Ala	328	.	.	B	B	.	.	.	1.12	.	*	F	1.92	3.71
Arg	329	.	.	B	.	.	T	.	1.34	.	*	F	2.66	4.29
Gln	330	.	.	.	.	T	T	.	1.89	.	.	F	3.40	2.21
Asp	331	.	.	.	.	T	T	.	1.60	.	*	F	3.06	2.17
Asp	332	.	.	.	.	T	T	.	1.24	.	*	F	2.72	1.10
Ala	333	.	.	.	.	T	.	.	0.94	.	.	.	1.58	0.99
Gly	334	.	.	B	B	.	.	.	0.17	.	.	.	0.64	0.42
Met	335	.	.	B	B	.	.	.	-0.64	.	.	.	-0.60	0.13
Tyr	336	.	.	B	B	.	.	.	-0.99	.	.	.	-0.60	0.11
Ile	337	.	.	B	B	.	.	.	-1.58	.	*	.	-0.60	0.11
Cys	338	.	.	B	B	.	.	.	-0.99	.	.	.	-0.60	0.11
Leu	339	.	.	B	B	.	.	.	-0.95	.	.	.	-0.60	0.11
Gly	340	.	.	B	.	.	T	.	-0.96	.	.	.	-0.20	0.24
Ala	341	.	.	B	.	.	T	.	-1.06	.	.	.	-0.20	0.43
Asn	342	.	.	.	.	.	T	C	-0.41	.	.	.	0.00	0.52
Thr	343	.	.	.	.	.	T	C	-0.04	.	.	.	0.00	0.82
Met	344	.	.	B	B	.	.	.	0.07	*	*	.	-0.45	1.09
Gly	345	.	.	B	B	.	.	.	0.52	*	*	.	-0.60	0.59
Tyr	346	.	.	B	B	.	.	.	0.81	*	.	.	-0.60	0.80
Ser	347	.	.	B	B	.	.	.	0.22	*	.	.	-0.15	1.08
Phe	348	.	.	B	B	.	.	.	-0.17	*	*	.	-0.15	1.11
Arg	349	.	.	B	B	.	.	.	-0.38	*	*	.	-0.60	0.61
Ser	350	.	.	B	B	.	.	.	-0.34	*	.	.	-0.60	0.38
Ala	351	.	.	B	B	.	.	.	-0.96	*	*	.	-0.60	0.63

FIG. 4N

21/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini_ Surto_
Phe	352			B	B				-1.47	*	.	.	-0.60	0.24
Leu	353			B	B				-0.98	*	.	.	-0.60	0.15
Thr	354			B	B				-1.09	.	.	.	-0.60	0.22
Val	355			B	B				-1.00	.	.	.	-0.60	0.43
Leu	356			B			T		-0.37	.	.	.	0.10	0.81
Pro	357					T	T		0.12	.	*	F	1.74	1.12
Asp	358					T			0.93	.	*	F	2.08	2.33
Pro	359						T	C	0.90	.	*	F	2.52	4.90
Lys	360							C	1.54	.	*	F	2.66	3.14
Pro	361					T			2.14	.	.	F	3.40	2.90
Gln	362					T			1.50	.	.	F	2.76	2.90
Gly	363						T		0.91	.	*	F	2.02	1.08
Pro	364			B					0.82	.	.	F	0.93	0.70
Pro	365			B					0.48	.	.	F	0.39	0.55
Val	366			B					0.39	.	.	F	0.05	0.74
Ala	367			B					0.03	.	.	F	0.05	0.64
Ser	368			B					-0.16	.	.	F	0.25	0.55
Ser	369			B					-0.26	.	.	F	0.34	0.75
Ser	370			B					-0.34	.	.	F	0.58	1.08
Ser	371			B				C	-0.30	.	.	F	1.47	1.08
Ala	372			B					0.08	.	.	F	0.41	0.66
Thr	373					T			0.09	.	.	F	0.90	0.77
Ser	374							C	0.18	.	.	F	0.31	0.60
Leu	375							C	-0.38	.	.	.	0.27	0.92
Pro	376			B			T		-0.93	.	.	.	-0.02	0.47

FIG. 40

22/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyte_ Hydro	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi	James_ Antig	Emini_ Surfa
Trp	377	.	.	B	.	.	T	.	-1.23	.	.	.	-0.11	0.26
Pro	378	.	.	B	.	.	T	.	-1.27	.	*	.	-0.20	0.22
Val	379	.	.	B	B	.	.	.	-1.85	.	*	.	-0.60	0.14
Val	380	.	.	B	B	.	.	.	-1.26	.	*	.	-0.60	0.09
Ile	381	.	.	B	B	.	.	.	-1.63	.	.	.	-0.60	0.09
Gly	382	.	.	B	.	.	.	.	-1.69	.	.	.	-0.40	0.13
Ile	383	.	.	B	.	.	.	.	-2.07	.	.	.	-0.40	0.17
Pro	384	.	.	B	.	.	T	.	-2.07	.	.	.	-0.20	0.25
Ala	385	.	.	B	.	.	T	.	-1.91	.	.	.	-0.20	0.19
Gly	386	.	.	B	.	.	T	.	-1.91	.	.	.	-0.20	0.23
Ala	387	.	.	B	.	.	T	.	-2.38	.	.	.	-0.20	0.10
Val	388	.	.	B	B	.	.	.	-1.83	.	.	.	-0.60	0.09
Phe	389	.	.	B	B	.	.	.	-1.93	.	.	.	-0.60	0.09
Ile	390	.	.	B	B	.	.	.	-2.16	.	.	.	-0.60	0.12
Leu	391	.	.	B	B	.	.	.	-2.62	.	.	.	-0.60	0.14
Gly	392	.	.	B	B	.	.	.	-2.84	.	.	.	-0.60	0.13
Thr	393	.	.	B	B	.	.	.	-2.28	.	.	.	-0.60	0.15
Leu	394	.	.	B	B	.	.	.	-2.39	.	.	.	-0.60	0.19
Leu	395	.	.	B	B	.	.	.	-2.17	.	*	.	-0.60	0.16
Leu	396	.	.	B	B	.	.	.	-1.36	.	*	.	-0.60	0.06
Trp	397	.	.	B	B	.	.	.	-1.60	.	.	.	-0.60	0.13
Leu	398	.	.	B	B	.	.	.	-1.29	.	*	.	-0.60	0.15
Cys	399	.	.	B	B	.	.	.	-0.43	.	*	.	-0.60	0.32
Gln	400	.	.	.	B	T	.	.	0.42	.	*	.	-0.20	0.61
Ala	401	.	.	.	B	T	.	.	1.02	.	.	.	1.19	1.49

FIG. 4P

23/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyle_ Hydro	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi	James_ Anlig	Emini Surfo
Gln	402	.	.	.	B	T	.	.	0.64	*	.	F	1.98	4.30
Lys	403	.	.	.	.	T	.	.	1.14	*	.	F	2.52	1.33
Lys	404	.	.	.	.	.	T	C	1.60	+	.	F	2.86	1.90
Pro	405	.	.	.	.	T	T	.	1.01	*	.	F	3.40	1.70
Cys	406	.	.	.	.	T	T	.	1.39	.	.	F	2.91	0.86
Thr	407	.	.	.	.	.	T	.	0.80	.	.	F	1.87	0.66
Pro	408	.	.	B	.	.	.	.	0.54	.	.	F	0.73	0.43
Ala	409	.	.	B	.	.	.	.	0.29	.	.	F	0.54	1.25
Pro	410	.	.	B	.	.	.	.	-0.31	.	.	F	0.20	1.34
Ala	411	.	.	B	.	.	.	C	0.14	.	.	F	0.25	0.71
Pro	412	.	.	B	.	.	.	.	0.11	.	.	F	0.48	1.09
Pro	413	.	.	B	.	.	.	.	0.29	.	.	F	0.61	0.70
Leu	414	.	.	B	.	.	.	.	0.99	.	.	F	1.09	0.94
Pro	415	.	.	B	.	.	T	.	0.99	.	.	F	2.12	1.19
Gly	416	.	.	.	.	T	T	.	1.37	.	.	F	2.80	1.19
His	417	.	.	.	.	.	T	C	1.23	.	.	F	2.32	2.24
Arg	418	.	.	.	.	.	T	C	1.13	.	.	F	1.84	1.43
Pro	419	.	.	.	.	.	T	C	1.36	*	.	F	1.76	2.09
Pro	420	.	.	.	B	T	T	.	0.76	*	.	F	1.68	1.55
Gly	421	.	.	B	.	.	T	.	1.10	*	.	F	0.85	0.65
Thr	422	.	.	B	.	.	T	.	1.24	*	.	F	0.85	0.70
Ala	423	.	.	B	.	.	.	.	0.83	*	.	F	0.99	0.89
Leu	424	.	.	B	.	.	.	.	0.70	*	.	F	1.78	1.21
Asp	425	.	.	B	.	.	T	.	0.91	*	.	F	2.17	0.83
Arg	426	.	.	B	.	.	T	.	1.30	*	.	F	2.66	1.37
Ser	427	.	.	.	.	T	T	.	1.61	*	.	F	3.40	3.32

FIG. 4Q

24/26

Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyle_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Gly	428	.	.	.	.	T	T	.	1.39	*	.	F	3.06	3.32
Asp	429	.	.	.	.	T	T	.	1.99	*	.	F	2.69	1.40
Lys	430	.	.	.	.	.	.	.	1.69	*	.	F	2.52	1.61
Asp	431	.	.	.	.	.	.	C	0.77	*	.	F	2.15	2.18
Leu	432	.	.	B	.	.	T	.	0.48	*	.	F	1.98	1.08
Pro	433	.	.	B	.	.	T	.	0.23	*	.	F	1.70	0.55
Ser	434	.	.	B	.	.	.	.	-0.58	.	.	F	0.93	0.33
Leu	435	.	.	B	.	.	.	.	-0.92	.	.	.	0.31	0.33
Ala	436	.	.	B	.	.	.	.	-1.51	.	.	.	-0.06	0.29
Ala	437	.	.	B	.	.	.	.	-1.04	.	.	.	-0.23	0.22
Leu	438	.	.	B	.	.	.	.	-1.04	.	.	.	-0.40	0.26
Ser	439	.	.	B	.	.	.	.	-1.09	.	.	.	-0.40	0.40
Ala	440	.	.	B	.	.	.	.	-1.13	.	.	F	0.05	0.39
Gly	441	.	.	.	.	.	T	C	-0.89	.	.	F	0.15	0.35
Pro	442	.	.	.	.	T	T	.	-1.11	.	.	F	0.65	0.26
Gly	443	.	.	.	.	T	T	.	-0.97	.	.	F	0.35	0.21
Val	444	.	.	.	.	.	T	C	-0.67	.	.	.	0.00	0.11
Gly	445	.	A	B	.	.	.	.	-0.08	.	.	.	-0.30	0.13
Leu	446	.	A	B	.	.	.	.	0.23	.	.	.	0.30	0.22
Cys	447	.	A	B	.	.	.	.	0.10	.	.	.	0.64	0.41
Glu	448	.	A	B	.	.	.	.	0.14	.	.	.	0.98	0.41
Glu	449	.	A	.	.	T	.	.	0.79	.	.	F	1.87	0.67
His	450	.	.	.	.	T	T	.	0.54	.	.	F	3.06	1.92
Gly	451	.	.	.	.	T	T	.	0.77	.	.	F	3.40	1.12
Ser	452	.	.	.	.	.	T	C	1.22	.	.	F	2.41	0.65
Pro	453	.	.	.	.	.	T	C	1.22	.	.	F	1.47	0.74

FIG. 4R

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Res	Pos	Garni_ Alpha	Chou- Alpha	Garni_ Beta	Chou- Beta	Garni_ Turn	Chou- Turn	Garni_ Coil	Kyte- Hydro	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi	James_ Anti	Emini_ Surfo
Ala	454	.	A	.	.	.	.	C	1.19	.	.	F	0.88	1.30
Ala	455	.	A	B	.	.	.	.	0.41	.	.	F	0.34	1.32
Pro	456	.	A	B	.	.	.	.	-0.06	.	.	F	-0.45	0.70
Gln	457	.	A	B	.	.	.	.	-0.10	.	.	.	-0.60	0.57
His	458	.	A	B	.	.	.	.	-0.10	.	.	.	-0.60	0.56
Leu	459	.	A	B	.	.	.	.	0.14	.	.	.	-0.60	0.56
Leu	460	.	A	B	.	.	.	.	0.52	.	.	.	-0.60	0.32
Gly	461	.	.	B	.	.	T	.	-0.12	.	.	F	-0.05	0.37
Pro	462	.	.	B	.	.	T	C	-0.71	.	.	F	0.15	0.33
Gly	463	.	.	.	.	.	T	C	-1.02	.	.	F	0.15	0.40
Pro	464	.	.	B	.	.	T	.	-0.42	.	.	F	0.25	0.40
Val	465	.	.	B	.	.	.	.	0.43	.	.	F	0.05	0.40
Ala	466	.	.	B	.	.	.	.	-0.03	.	.	F	0.65	0.81
Gly	467	.	.	B	.	.	T	.	-0.07	.	.	F	0.45	0.43
Pro	468	.	.	B	.	.	T	.	0.07	.	*	F	0.35	0.92
Lys	469	.	.	B	.	.	T	.	0.32	*	*	F	1.00	1.40
Leu	470	.	.	B	.	.	T	.	0.37	*	*	F	1.80	2.83
Tyr	471	.	.	B	.	.	T	.	0.71	*	*	F	2.00	1.51
Pro	472	.	.	B	.	.	T	.	0.74	*	*	F	1.20	1.18
Lys	473	.	.	B	.	.	T	.	0.96	*	*	F	0.70	2.07
Leu	474	.	.	B	.	.	T	.	0.02	*	*	F	0.80	2.21
Tyr	475	.	.	B	B	.	.	.	0.80	*	*	F	0.20	1.00
Thr	476	.	.	B	B	.	.	.	0.73	*	*	F	-0.15	0.68
Asp	477	.	.	B	B	.	.	.	0.91	*	*	.	-0.45	1.19
Ile	478	.	.	B	B	.	.	.	0.56	*	*	.	-0.45	1.03
His	479	.	.	B	B	.	.	.	1.33	.	*	.	-0.15	1.03

FIG. 4S

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Res	Pos	Garni_ Alpha	Chou_ Alpha	Garni_ Beta	Chou_ Beta	Garni_ Turn	Chou_ Turn	Garni_ Coil	Kyle_ Hydro	Eisen_ Alpha	Eisen_ Beta	Korpl_ Flexi	James_ Antig	Emini_ Surfa
Thr	480	.	.	B	B	.	.	.	1.27	.	.	.	-0.30	0.84
His	481	.	.	.	B	.	.	C	1.54	.	.	.	-0.25	1.74
Thr	482	.	.	.	B	.	.	C	1.24	.	*	.	-0.25	1.74
His	483	.	.	.	.	.	T	C	2.10	.	.	.	0.45	1.61
Thr	484	.	.	.	.	.	T	C	1.82	.	.	.	0.45	1.61
His	485	.	.	.	.	.	T	C	2.10	.	.	.	0.45	1.61
Ser	486	.	.	.	.	.	T	C	1.83	.	.	.	0.45	1.61
His	487	.	.	.	.	.	T	C	2.11	.	.	.	0.45	1.50
Thr	488	.	.	.	.	.	T	C	1.29	.	.	.	0.45	1.50
His	489	.	.	.	.	.	T	C	1.60	.	.	.	0.51	0.83
Ser	490	.	.	.	.	.	T	C	1.29	.	*	.	0.87	1.06
His	491	.	.	.	.	.	.	C	1.63	.	*	.	1.33	0.72
Val	492	.	.	.	.	.	.	C	0.81	.	.	.	1.99	1.06
Glu	493	.	.	.	.	T	.	.	1.09	.	*	F	2.10	0.59
Gly	494	.	.	.	B	T	.	.	1.12	.	*	F	1.69	0.59
Lys	495	.	.	.	B	T	.	.	1.39	*	*	F	1.63	1.37
Val	496	.	.	B	B	.	.	.	0.53	*	*	.	1.17	1.08
His	497	.	.	B	B	.	.	.	1.36	*	*	.	-0.09	0.76
Gln	498	.	.	B	B	.	.	.	1.11	.	*	.	-0.30	0.52
His	499	.	.	B	B	.	.	.	1.46	*	*	.	-0.45	1.10
Ile	500	.	.	B	B	.	.	.	0.74	*	*	.	-0.45	1.40
His	501	.	.	B	B	.	.	.	1.21	.	*	.	-0.60	0.43
Tyr	502	.	.	.	B	T	.	.	0.85	.	.	.	-0.20	0.41
Gln	503	.	.	.	B	T	.	.	0.47	.	.	.	-0.20	0.74
Cys	504	.	.	B	B	.	.	.	0.11	.	*	.	-0.60	0.70

FIG. 4T

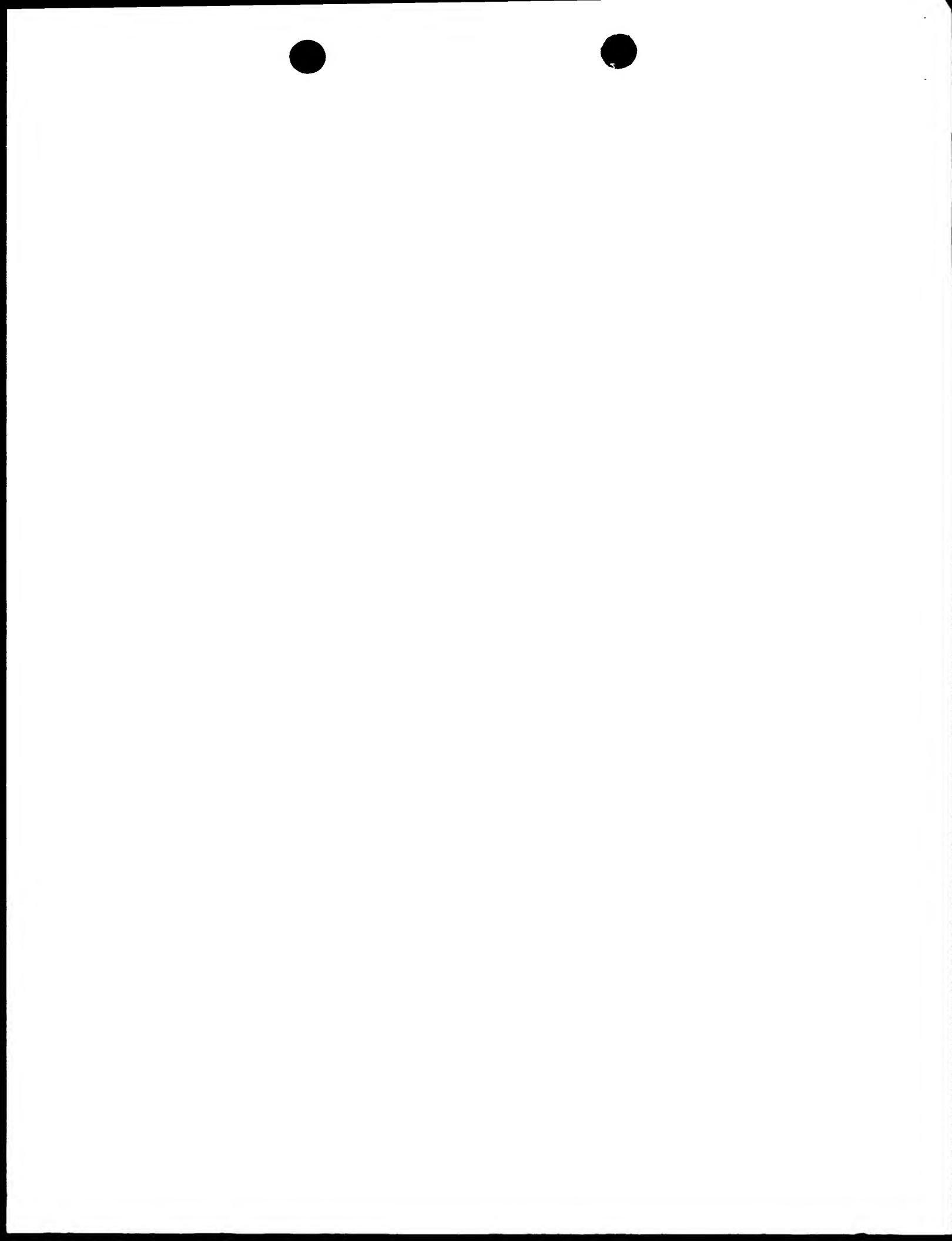


## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4239-55911	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/26689	International filing date (day/month/year) 29/09/2000	Priority date (day/month/year) 02/10/1999
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the report</li><li>II <input type="checkbox"/> Priority</li><li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li><li>IV <input type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li><li>VI <input checked="" type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li></ul>		
Date of submission of the demand  30/04/2001	Date of completion of this report  18.12.2001	
Name and mailing address of the international preliminary examining authority:   European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer  Siatou, E  Telephone No. +49 30 25901 327	





**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/26689

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-71 as originally filed

**Claims, No.:**

1-41 as originally filed

**Drawings, sheets:**

1/8-8/8 as originally filed

**Sequence listing part of the description, pages:**

1-17, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

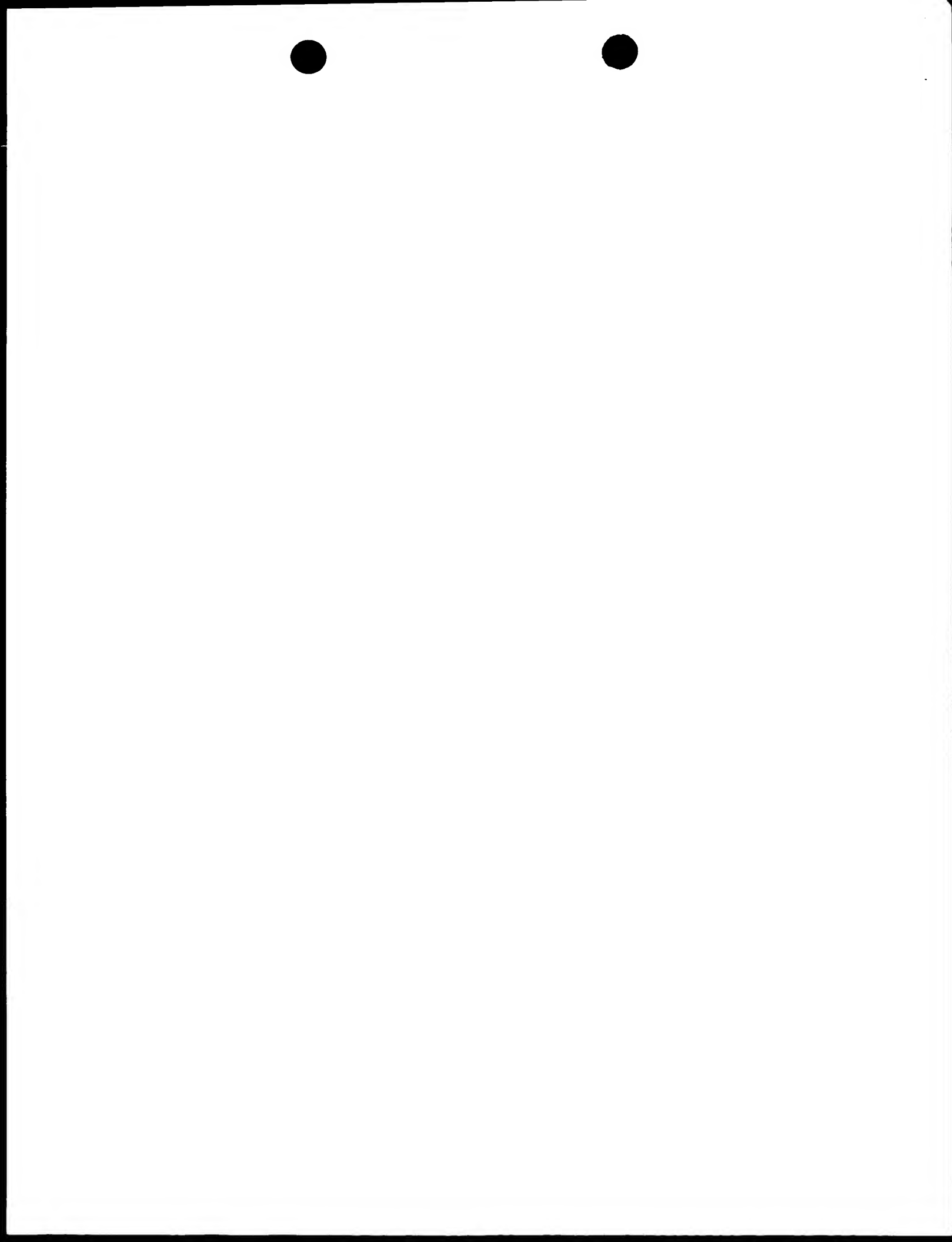
These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/26689

- ☐ the description,      pages:  
☐ the claims,      Nos.:  
☐ the drawings,      sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 1-26, 37-41 and 27-32 (partially) in respect of industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 1-26, 37-41 and 27-32 (partially) in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-5, 17, 20-21, 23, 25-26, 33-38 (all partially).
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims 7-22, 25-32, 40-41
	No: Claims 1-6, 23-24, 33-39
Inventive step (IS)	Yes: Claims 7-22, 25-32, 40-41
	No: Claims 1-6, 23-24, 33-39
Industrial applicability (IA)	Yes: Claims 27-32 (partially)
	No: Claims

**2. Citations and explanations  
see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**





**Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-26, 27-32, as far as in vivo applications are concerned, and 37-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. An opinion will be given for those parts of the application which have been the subject of a search report, namely the parts relating to the use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunoreactive sensitized T cells sensitized with FGF-5.

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The Applicant's attention is drawn to the fact that the present opinion expressed as to the novelty, inventive step and industrial applicability refers only to the matter for which an international search report has been drawn up.

Reference is made to the following documents:

D1: WO-A-9012597

D2: JP-A-10017599 (PAJ abstract)

Document D1 discloses pharmaceutical compositions comprising a conjugate of fibroblast growth factor (FGF) or a polypeptide reactive with an FGF receptor and a cytotoxic agent for treating a variety of FGF-mediated diseases, such as tumors. FGF-5 is explicitly mentioned (see claims 1-21 and page 5, lines 13-34). The subject matter of claims 1-6, 23-24 and 37-39 of the present invention is neither novel nor inventive (Art. 33(2) and 33(3) PCT).

Document D2 (see abstract) discloses antibodies binding exclusively to FGF-5 and



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/26689

their use in detecting the presence of FGF-5. The subject matter of claims 33-36 is neither novel nor inventive (Art. 33(2) and 33(3) PCT).

None of the cited prior art documents discloses or suggests the subject matter of claims 7-22, 25-32 and 40-41. The subject matter of these claims meets the requirements of Art. 33(2) and 33(3) PCT.

**Re Item VI**

Certain documents cited

Certain published documents (Rule 70.10)

Application No

Patent No

Publication date

(day/month/year)

Filing date

(day/month/year)

Priority date (valid claim)

(day/month/year)

WO-A-0024756

04.05.00

17.06.99

23.10.98

WO-A-9955861

04.11.99

15.04.99

28.04.98

**Re Item VIII**

Certain observations on the international application

Claim1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Moreover, and as already stated in the search phase, support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT is to be found for only a very small number of compounds/products within the scope of the present application, namely use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunoreactive sensitized T cells sensitized with FGF-5.



**INTERNATIONAL PRELIMINARY**

International application No. PCT/US00/26689

**EXAMINATION REPORT - SEPARATE SHEET**

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## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 17 July 2001 (17.07.01)	
<b>International application No.</b> PCT/US00/26689	<b>Applicant's or agent's file reference</b> 4239-55911
<b>International filing date</b> (day/month/year) 29 September 2000 (29.09.00)	<b>Priority date</b> (day/month/year) 02 October 1999 (02.10.99)
<b>Applicant</b> HANADA, Ken-Ichi et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

30 April 2001 (30.04.01)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b>  H. Zhou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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DT155 19 2002

16 92

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
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(10) International Publication Number  
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TECH CENTER 1600/2900

JUN 1 8 2002

(51) International Patent Classification: **A61K 38/18**,  
C07K 14/50, A61K 39/395, C07K 16/22

(74) Agent: NOONAN, William, D., Klarquist, Sparkman,  
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(US).

(21) International Application Number: PCT/US00/26689

(22) International Filing Date:  
29 September 2000 (29.09.2000)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
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DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/157,103 2 October 1999 (02.10.1999) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): THE  
GOVERNMENT OF THE UNITED STATES OF  
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VICES [US/US]; The National Institutes of Health,  
Office of Technology Transfer, Suite 325, 6011 Executive  
Boulevard, Rockville, MD 20852-3804 (US).

Published:  
*with international search report*

(88) Date of publication of the international search report:  
10 May 2002

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): HANADA, Ken-ichi  
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Court, Silver Spring, MD 20904 (US).

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

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WO 01/25271 A3

(54) Title: FIBROBLAST GROWTH FACTOR-5 (FGF-5) IS A TUMOR ASSOCIATED T-CELL ANTIGEN

(57) Abstract: Disclosed herein are methods for treating tumors which express or over-express the tumor associated antigen (TAA) fibroblast growth factor 5 (FGF-5), including renal cell carcinoma (RCC) and carcinoma of the prostate and breast. Methods include modulating an immune response, such as increasing an immune response, or modulating FGF-5 expression or activity. The disclosure also includes methods of determining if a subject has an enhanced susceptibility to a disease associated with abnormal FGF-5 expression.

FOR INFORMATION ONLY

APR 28 2010

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# INTERNATIONAL SEARCH REPORT

Internatic Application No  
PCT/US 00/26689

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K38/18 C07K14/50 A61K39/395 C07K16/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X,P	WO 00 24756 A (HUNAN GENOME SCIENCES INC.) 4 May 2000 (2000-05-04) claims 1-23	1-41
X,P	WO 99 55861 A (EISAI CO. LTD.) 4 November 1999 (1999-11-04)  claims 1-19,23,24 page 42, line 10 - line 3 page 46, line 20 -page 47, line 26	1-5, 9-14,23, 24, 27-32, 37-40
X	WO 90 12597 A (THE SALK INSTITUTE FOR BIOLO) 1 November 1990 (1990-11-01) the whole document	1-6,23, 24,37-39

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

### \* Special categories of cited documents

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*S\* document member of the same patent family

Date of the actual completion of the international search

9 July 2001

Date of mailing of the international search report

20/07/2001

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Siatou. E



## INTERNATIONAL SEARCH REPORT

Internatic Application No  
PCT/US 00/26689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 05, 30 April 1998 (1998-04-30) & JP 10 017599 A (POLA CHEM IND INC), 20 January 1998 (1998-01-20) abstract ---	33-36
A	ZHAN X ET AL: "THE HUMAN FGF-5 ONCOGENE ENCODES A NOVEL PROTEIN RELATED TO FIBROBLAST GROWTH FACTORS" MOLECULAR AND CELLULAR BIOLOGY, US, WASHINGTON, DC, vol. 8, no. 8, 1 August 1988 (1988-08-01), pages 3487-3495, XP002034597 ISSN: 0270-7306 abstract ---	1-41
A	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; YAMANAKA K. ET AL: "Expression of fibroblast growth factors in human non-papillary renal cell carcinoma: Correlation with tumor progression." retrieved from STN Database accession no. 1999207619 XP002171451 abstract & INTERNATIONAL JOURNAL OF CLINICAL ONCOLOGY, (1999) 4/2 (74-77). , ---	1-41
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOSHIMURA, KOJI ET AL: "Messenger ribonucleic acids for fibroblast growth factors and their receptor in bladder and renal cell carcinoma cell lines" retrieved from STN Database accession no. 124:339650 HCA XP002171452 abstract & CANCER LETT. (SHANNON, IREL.) (1996), 103(1), 91-7 . --- -/--	1-41



# INTERNATIONAL SEARCH REPORT

Internatic Application No  
PCT/US 00/26689

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE. COLUMBUS, OHIO, US: WERNER, SABINE ET AL: "Fibroblast growth factor 5 proto-oncogene is expressed in normal human fibroblasts and induced by serum growth factors" retrieved from STN Database accession no. 116:35063 HCA XP002171453 abstract &amp; ONCOGENE (1991), 6(11), 2137-44 ,</p> <p>-----</p>	1-41





## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 1-26, 37-41 and 27-32, as far as they refer to an invivo method, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

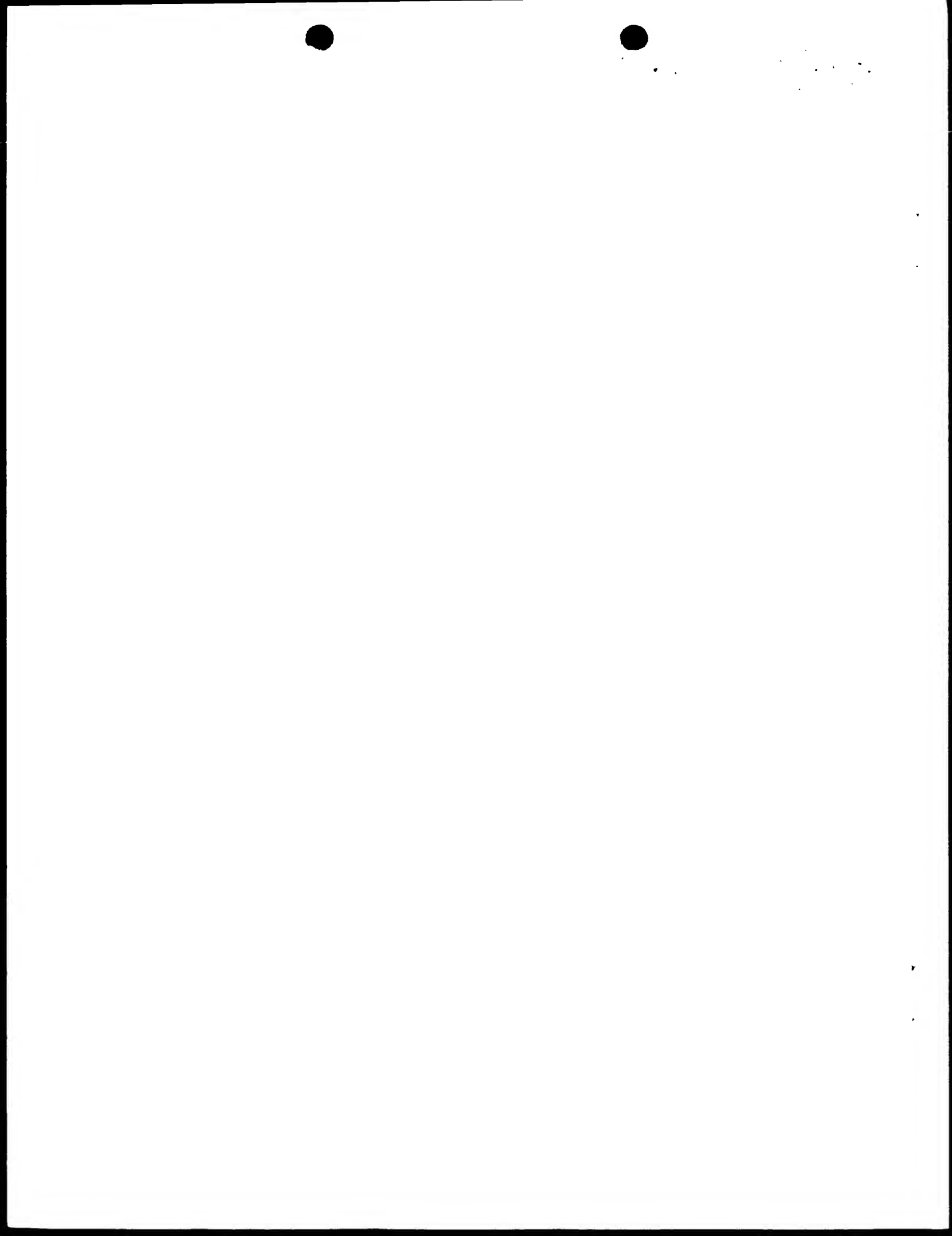
Although claims 33-36 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## Continuation of Box I.2

Present claims 1-5, 17, 20-21, 23, 25-26, 33-38 relate to a compound defined by reference to a desirable characteristic or property, namely modulation of FGF-5 expression/activity or modulation of immune response to FGF-5.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunoreactive sensitized T cells sensitized with FGF-5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/26689

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